Where Ct is the concentration of formoterol in the protein compartment (total drug = free + bound) and Cf is that in the buffer compartment (free drug) at the end of the dialysis. The volume in each compartment of the cell after dialysis was found to be unchanged (no volume shift occurred from buffer to serum).

Results: Stability studies indicated that formoterol was unstable in HSA S1 at 37° C. Thus, it was incubated 5 hours at 5 °C. All other incubations were 6 hours at 37° C. In the first HSA S3 experiment, the binding of formoterol to albumin remained relatively constant over the concentration range of 5 to 500 ng/mL (31.1% to 37.7%). Results from further HSA studies are presented in Table 6. Formoterol binding to α-1-acid glycoprotein (AAG) and γ globulin (GG) is described in Table 7.

Table 6. Binding of Formoterol to Human Serum Albumins (HSA S1, S2, and S3) After Equilibrium Dialysis at 37° C for 6 hours

Formoterol Conc.	*HSA 1*	*HSA2*	*HSA3*
50 ng/mL	34.2[1]	33.9	31.9
100 ng/mL	—[2]	32.3	34.2

Table 7. Binding of Formoterol to to α-1-Acid Glycoprotein (AAG) and γ Globulins (GG) After Equilibrium Dialysis at 37° C for 6 hours

Formoterol Conc.	*GG*	*AAG*
10.4 ng/mL	1.9%	11.9%
50 ng/mL	3.2%	6.4%
100 ng/mL	4.2%	3.2%

Conclusions: Since formoterol is not highly protein bound, changes in AAG, GG or albumin due to stress or various disease states should not result in clinically significant changes in formoterol protein binding or subsequent changes in drug disposition.

[1] Incubated 5 hours at 5 °C
[2] Not conducted

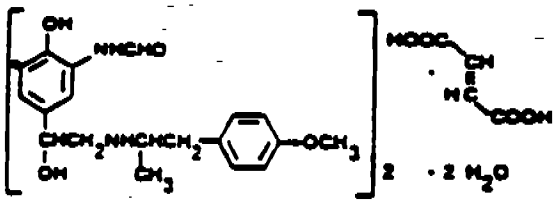
In Vitro Characterization of the Human Cytochrome P450 Isozyme(s) Catalyzing the O-Demethylation of Formoterol

Protocol No. 96-7015 **Volume** 1.73 **Pages** 155 - 201

Objective To investigate the O-demethylation of formoterol using human liver microsomes and identify the responsible isozyme(s).

Materials

- [^{3}H]-formoterol (Batch 612.5B-7, 2.67 MBq/mg). Radiochemical purity was ≥ 97%.



Formoterol fumarate
(I•fumarate)

• ^{3}H-label

- The following cytochrome P450 isozyme-specific inhibitors:
  α-napthoflavone (1A2), furafylline (1A2), pilocarpine (2A6), 8-methoxypsoralen (2A6), sulphaphenazole (2C9/10), tranylcypromine (2C19), quinidine (2D6), 4-methylpyrazole (2E1), ketoconazole (3A), troleandomycin (3A)
- The following human liver microsomes:
  (Pool A) prepared from pieces of liver from 8 donors.
  (Pool B) Reaction Phenotyping Kit. In these microsomes the following CYP450 specific activities have been provided by the provider [redacted]. CYP2C9, 2C19, 2D6 and 2A6. The pre-determined marker enzyme activities were compared to the formoterol O-demethylation activity as catalyzed by the human liver microsomes.
- The following recombinant human microsomes:
  (from human recombinant lymphoblastoid cell lines) control microsomes, CYP2C19, 1A2, control + red,[3] 2A6 + red, 2E1 + red, 2D6 + red, 2C9 + red, 3A4 + red
  (from baculovirus infected insect cell lines) CYP2C19 + red

***In vitro* Incubations** Incubations of 200 µL were prepared from: microsomal protein, a NADPH-regenerating system, [^{3}H]-formoterol and a 0.1 mol/L phospahte buffer (pH 7.4). The reactions were equilibrated at 37° C in a shaking water bath and started by the addition of [^{3}H]-formoterol. Samples were incubated for up to 60 minutes and where applicable, inhibitors were added at appropriate concentrations. Control incubations were performed with heat inactivated microsomes. All incubations were

[3] +red: also contains human cytochrome P450 oxido-reductase

quenched by the addition of ice-cold acetonitrile and subsequent centrifugation. Michaelis-Menten kinetic parameters were calculated according to:

$$V_0 = (V_{max} \cdot S)/(S+K_m)$$

where V_0 is the rate of the reaction at substrate concentration S, and K_m and V_{max} are the Michaelis constants for the reaction. In the presence of a competitive inhibitor, the Michaelis-Menten equation is:

$$V_0 = (V_{max} \cdot S)/(S+K_m(1+I/K_i))$$

With a non-competitive inhibitor, the equation is modified to:

$$V_0 = (V_{max} \cdot S)/((S+K_m) \cdot (1+I/K_i))$$

Results

Human Liver Microsome Experiments A linear relationship was observed between the production of O-desmethyl-formoterol in incubations of 400 µmol/L [^{3}H]-formoterol (in Protocol 54, which was not formally reviewed, after inhalation of a single 120 µg dose, peak formoterol plasma concentrations of approximately 266 pmol/L were observed) and protein concentrations of 1 - 3 mg/mL. Further kinetic studies were conducted at a protein concentration of 2 mg/mL. Under these conditions, the reaction rate was dependent on the [^{3}H]-formoterol concentration with Michaelian single enzyme kinetics in the range of 10 - 100 µmol/L formoterol. The apparent kinetic parameters were: K_m=60.1 ± 9.0 µmol/L and V_{max}=103.3 ± 7.6 pmol/min•mg protein. Microsomes also catalyzed the formation of an unknown metabolite with a ——————— retention time longer than that of formoterol. To determine which CYP450 isozymes are responsible for the O-demethylation of formoterol, further [^{3}H]-formoterol, human liver microsome studies were conducted with selected CYP450 isozyme-specific inhibitors using concentrations of two and 10 times literature K_i values. Under these experimental conditions, only tranylcypromine (CYP2C19-specific inhibitor) distinctly inhibited formoterol O-demethylation in human liver microsomes. Of the other inhibitors tested, sulphaphenazole (CYP2C9) and pilocarpine (CYP2A6) slightly inhibited formoterol O-demethylation (9.5% and 8%, respectively at 2 K_i and 21.8% and 12.6%, respectively at 10 K_i). None of the other specific inhibitors had an appreciable effect on formoterol O-demethylation. Further experiments were conducted using recombinant microsomes expressing one single human cytochrome P450 isozyme. From the seven isozymes tested, CYP2A6, 2C9, 2C19 and 2D6 catalyzed the O-demethylation of formoterol. Additionally, CYP2D6 catalyzed the formation of the unknown metabolite described above. No formoterol O-demethylation was observed in incubations conducted with recombinant microsomes not containing CYP450 isozymes.

Conclusion

Based on these *in vitro* findings, it appears that formoterol is O-demethylated by CYP2D6, 2C19, 2C9 and 2A6.

Evaluation of a new chemical entity, CGP 25827, as an inhibitor of human P450 enzymes[4]

Protocol No. —042496 **Volume** 1.73 **Pages** 203 - 285

Objective To evaluate the ability of formoterol to inhibit the major P450 enzymes in human liver microsomes.

Materials & Methods

Studies were designed to determine the inhibitory constant (K_i) for formoterol for each of the major P450 enzymes found in human liver microsomes. This potential was assessed by evaluating formoterol's inhibition of the following human P450 catalyzed reactions:

- **CYP1A2** (7-Ethoxyresorufin O-dealkylation)
- **CYP2A6** (Coumarin 7-hydroxylation)
- **CYP2C9** (Tolbutamide methyl-hydroxylation)
- **CYP2C19** (S-Mephenytoin 4'-hydroxylation)
- **CYP2D6** (Dextromethorphan O-demethylation)
- **CYP2E1** (Chlorzoxazone 6-hydroxylation)
- **CYP3A4/5** (Testosterone 6β-hydroxylation)
- **CYP4A9/11** (Lauric acid 12-hydroxylation)

The concentrations of formoterol studied were 0.2, 2.0, 10.0 and 20.0 μM. A pool of human liver microsomes (from 7 individuals) with known enzymatic capability was used to evaluate formoterol's ability to inhibit P450 mediated catalysis.

To examine formoterol's ability to act as a reversible inhibitor, it was added to human liver microsomes together with the marker substrate. Duplicate reactions were initiated with NADPH. Marker substrate concentrations were $K_m/2$, K_m and $4K_m$. For each assay, a positive control (known competitive inhibitor was included). After the reaction was quenched data were analyzed to determine the type of inhibition (if any) and the inhibitory constant (K_i).

To examine the mechanism-based, non-competitive inhibition potential of formoterol, a pool of microsomes was pre-incubated with formoterol and NADPH to allow for the generation of metabolites which could irreversibly inhibit CYP450. An aliquot of the pre-incubated microsomes was removed and added to a new incubation containing the marker substrate and another incubation was carried out to measure the residual marker P450 activity. This procedure allowed a 10-20 fold formoterol dilution before the final marker substrate incubation, designed to minimize reversible inhibition effects. Thus, any inhibition observed was most likely mechanism-based.

[4] This study was not conducted in strict accordance with the FDA Good Laboratory Practice (GLP) regulations.

Method Details

CYP1A2 activity: 7-Ethoxyresorufin O-dealkylation

(reversible inhibition) 7-Ethoxyresorufin (0.25, 0.50, and 2.0μM) was added to each formoterol/microsome incubation.

(mechanism-based inhibition) After microsomal pre-incubation with the test article or furafylline, a 100 μL aliquot was added to each formoterol/microsome incubation mixture containing 0.5 μM 7-Ethoxyresorufin.

CYP2A6 activity: Coumarin 7-hydroxylation

(reversible inhibition) Coumarin (0.35, 0.70 and 2.8 μM) was added to each formoterol/microsome incubation.

(mechanism-based inhibition) After microsomal pre-incubation with the test article, a 50 μL aliquot was added to each formoterol/microsome incubation mixture containing 0.7 μM coumarin.

CYP2C9 activity: Tolbutamide hydroxylation

(reversible inhibition) Tolbutamide (180, 360 and 1440 μM) was added to each formoterol/microsome incubation.

(mechanism-based inhibition) After microsomal pre-incubation with the test article, a 20 μL aliquot was added to each formoterol/microsome incubation mixture containing 360 μM tolbutamide.

CYP2C19 activity: S-Mephenytoin 4'-hydroxylation

(reversible inhibition) S-Mephenytoin (17.5, 35 and 140 μM) was added to each formoterol/microsome incubation.

(mechanism-based inhibition) After microsomal pre-incubation with the test article, a 20 μL aliquot was added to each formoterol/microsome incubation mixture containing 35 μM S-Mephenytoin.

CYP2D6 activity: Dextromethorphan O-demethylation

(reversible inhibition) Dextromethorphan (2.5, 5 and 20 μM) was added to each formoterol/microsome incubation.

(mechanism-based inhibition) After microsomal pre-incubation with the test article, a 50 μL aliquot was added to each formoterol/microsome incubation mixture containing 5 μM dextromethorphan

CYP2E1 activity: Chlorzoxazone 6-hydroxylation

(reversible inhibition) Chlorzoxazone (15, 30 and 120 μM) was added to each formoterol/microsome incubation.

(mechanism-based inhibition) After microsomal pre-incubation with the test article, a 50 µL aliquot was added to each formoterol/microsome incubation mixture containing 30 µM chlorzoxazone.

CYP3A4/5 activity: Testosterone oxidation

(reversible inhibition) Testosterone (25, 50 and 200 µM) was added to each formoterol/microsome incubation.

(mechanism-based inhibition) After microsomal pre-incubation with the test article, a 50 µL aliquot was added to each formoterol/microsome incubation mixture containing 50 µM testosterone.

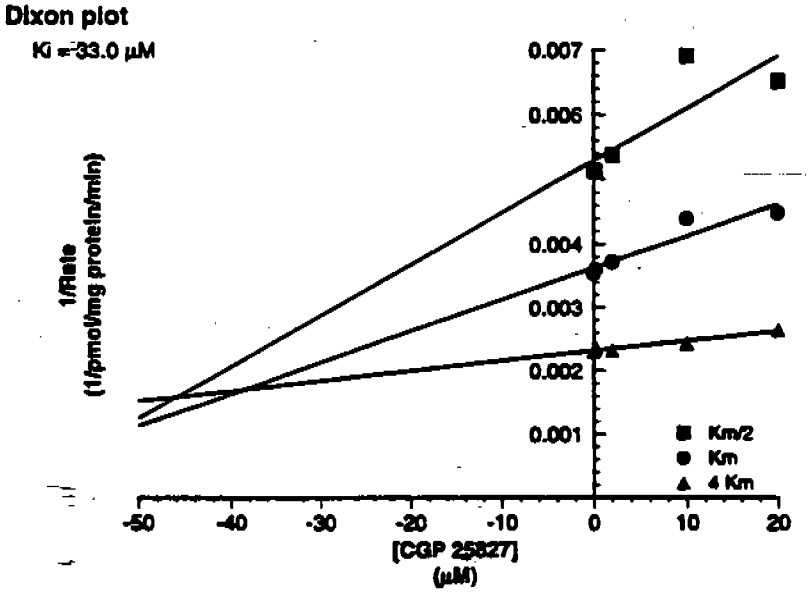
CYP4A9/11: Lauric acid 12-hydroxylation

(reversible inhibition) [^{14}C]-lauric acid (0.50 µCi/mL: 8.93, 15 and 60 µM) was added to each formoterol/microsome incubation.

(mechanism-based inhibition) After microsomal pre-incubation with the test article, a 80 µL aliquot was added to each formoterol/microsome incubation mixture containing 15 µM [^{14}C]-lauric acid.

Results

With the exception of the CYP2D6 Dextromethorphan O-demethylation experiment, formoterol showed no potential to inhibit major CYP450 mediated catalysis. In the dextromethorphan experiment, a K_i value of 33.0 µM was calculated. This would classify formoterol as a modest competitive inhibitor of CYP2D6. For sake of comparison, the positive control inhibitor for this experiment was quinidine, with an observed K_i value of 0.218 µM.



Conclusion

Under the experimental conditions evaluated, formoterol demonstrated the potential to inhibit only CYP2D6. The observed K_i value of 33.0 μM should be greater than anticipated plasma formoterol concentrations in patients receiving therapeutic doses of formoterol fumarate (in Protocol 54, after inhalation of a single 120 μg dose, peak formoterol plasma concentrations of approximately 266 pmol/L were observed). Thus, formoterol fumarate is not expected to inhibit the metabolism of concomitant CYP450-metabolized drugs to a clinically relevant extent.

Urinary excretion of the enantiomers of formoterol in healthy subjects after single-doses of CGP 25827A, using the dry powder ———device

Study No. — (US) 1996/08 **Volume** 1.73 **Pages** 65 - 113
Study Dates 10/5/92 - 11/11/92
Analytical Facility Ciba Geigy
Analysis Dates 6/28/94 - 11/11/94

Note: Protocol —— .01, conducted in 1992, was designed to assess the pharmacokinetics of racemic formoterol after administration with the ——— dry powder device (12, 24, 48 and 96 µg single-dose). At this time, only racemic formoterol was analyzed. In 1994, Ciba-Geigy developed an enantioselective method for the determination of formoterol enantiomers in urine. Therefore, it was decided to re-analyze the urine samples from this study. The results of that re-analysis are reviewed here.

OBJECTIVES To assess the pharmacokinetic behavior (urine) of the (R,R)- and (S,S)-enantiomers of formoterol.

FORMULATIONS Formoterol fumarate was diluted with lactose to arrive at a capsule with the required dosage strengths. The following formulations were used:

- Formoterol fumarate 6 µg/puff Batch 1077/1
- Formoterol fumarate 12 µg/puff Batch 1078/1
- Formoterol fumarate 24 µg/puff Batch 1079/1
- Placebo 0 µg/puff Batch 1076/1

Treatment A: 12 µg formoterol fumarate
Treatment B: 24 µg formoterol fumarate
Treatment C: 48 µg formoterol fumarate
Treatment D: 96 µg formoterol fumarate
Treatment E: Placebo

STUDY DESIGN This was a randomized, single-dose, double-blind, double-dummy five-period, crossover design trial comparing the urinary pharmacokinetics of formoterol after inhalation of 12 µg, 24 µg, 48 µg and 96 µg formoterol dry powder A total of 10 healthy, caucasian, non-smoking adult males, aged 20 - 55 years, were enrolled in this study. Each subject received Treatments A - E separated by a washout period of at least 5 days. Patients were required to abstain from the ingestion of foods and beverages containing caffeine from 12 hours prior to each drug administration until 24 hours thereafter. All subjects were trained for proper inhaler use within three days of the dosing. Subjects fasted overnight, and reported to the study facility 30 minutes before dosing began. After baseline monitoring, to include a urine collection, was—

[5] Different than that proposed for marketing

completed, a single dose of study medication was inhaled. Urine fractions were obtained 0-1, 1-2, 2-4, 4-8 and 8-24 hours after dosing. Concentrations of the (R,R)- and (S,S)-enantiomers of formoterol were measured using [redacted] assay with [redacted]

Assay Assay validation and performance data were not included in the study report. In the result section of the study report, it is stated that the analyses were performed without quality control samples, but instead summed the enantiomer concentrations and compared that to the racemic concentrations found in the previous analysis.

DATA ANALYSIS

Pharmacokinetic: - $A_{e\ (0\text{-}24hr)}$

RESULTS All 10 subjects completed all phases of the trial and were included in the analysis. Cumulative (R,R)- and (S,S)-formoterol excretion is presented in Figure 3. Excretion rates appear in Figure 4. In the 12 µg treatment group, urinary (R,R)- and (S,S)-formoterol fractions collected ($A_{e\ (0\text{-}24hr)}$) were 3.9% and 5.0% of the administered dose, respectively. In the 24 µg treatment group, urinary (R,R)- and (S,S)-formoterol fractions collected were 3.5% and 4.7% of the administered dose, respectively.

Figure 3. Cumulative Urinary Excretion (nmol) for (R,R)- and (S,S)-Formoterol After a Single 96 µg Dose

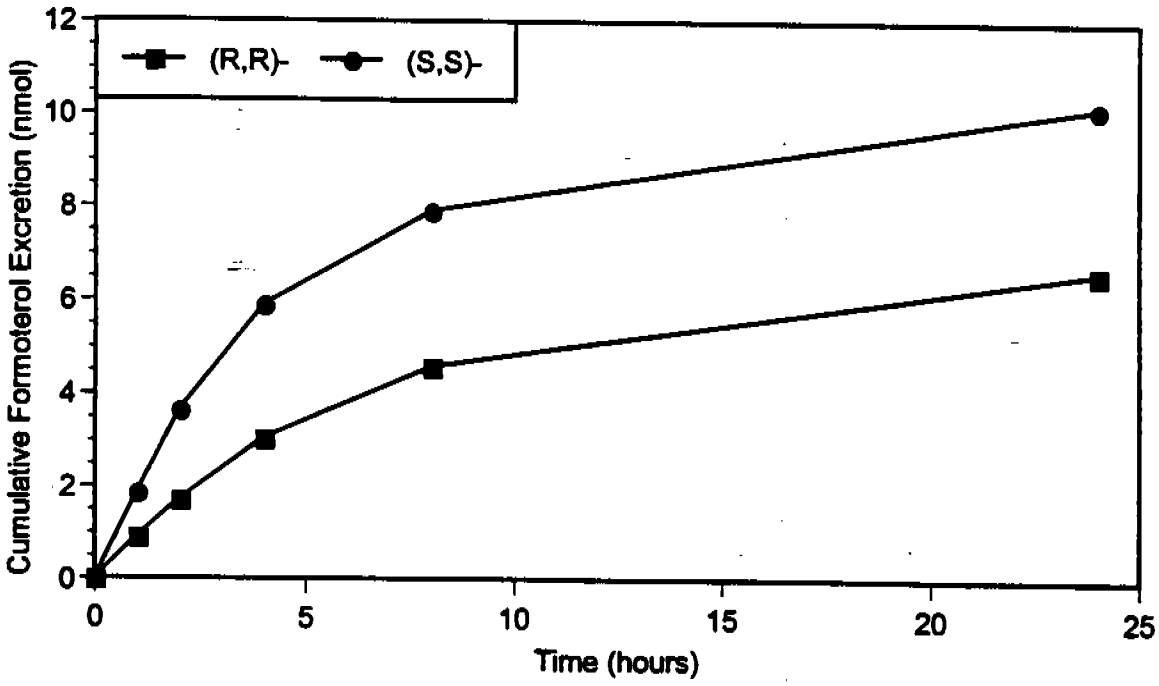
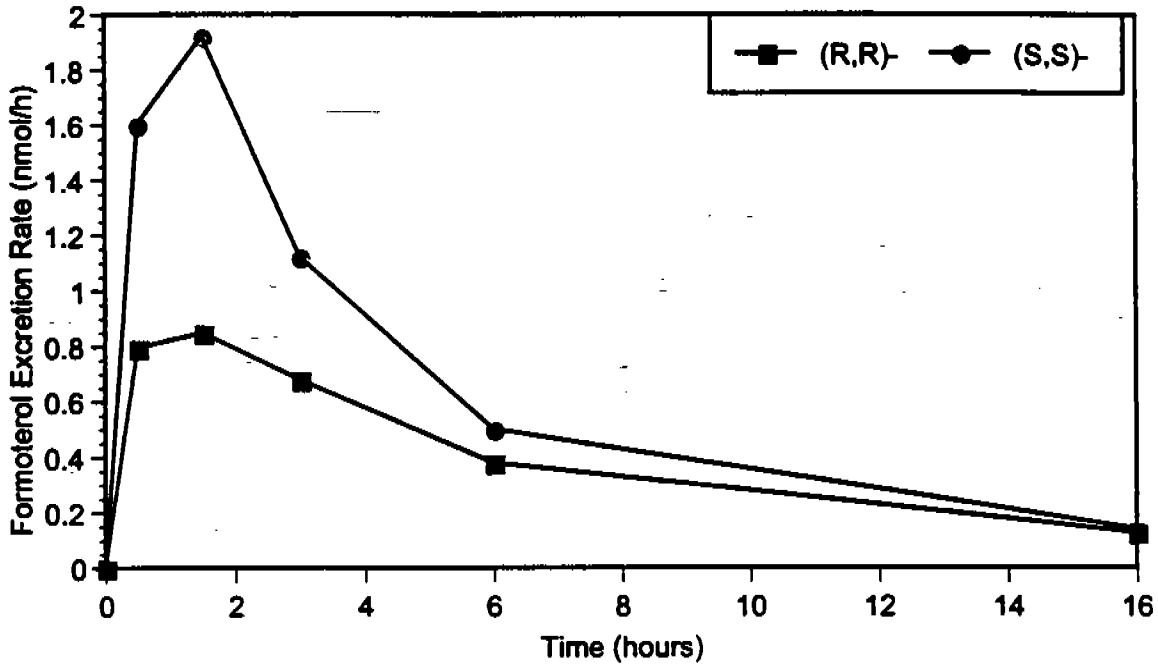


Figure 4. Urinary Excretion Rates (nmol/h) for (R,R)- and (S,S)-Formoterol After a Single 96 µg Dose



COMMENTS

1. Only summary assay validation and performance data were included in the study report. The sponsor stated that the analyses were performed without quality control samples, but instead summed the enantiomer concentrations and compared that to the racemic concentrations found in the previous analysis. This is an unacceptable practice and suggests that the analysis may have been done with far less than accepted good laboratory practices.
2. Previous formoterol studies indicated that a large fraction of systemic formoterol is present in the urine as a glucuronide. A more accurate analysis would have been possible if these samples were analyzed both before and after hydrolysis by α-glucuronidase.

CONCLUSION All conclusions reached here need to be considered in light of the absence of a fully validated assay. Additionally, since the excretion of the glucuronidated moiety was not assessed, only a small fraction of the total formoterol was measured. Data from this study suggest that the (S,S)-formoterol enantiomer may be excreted at a more rapid rate than the ((R,R)-enantiomer. Nevertheless, this analysis does not adequately address the issue of formoterol's chiral-specific elimination or interconversion.

Binding of Unchanged Drug to Plasma Protein

Report No. — F-1-4-6 **Volume** 1.73 **Pages** 115 - 125

Objectives: To assess the extent of binding of formoterol to plasma proteins using a ultracentrifugation method

Materials:

[^{3}H]-formoterol fumarate [redacted]
Formoterol fumarate (synthesized by the [redacted]

Pooled plasma derived from the blood of 3 healthy, male adults (age 30 -36 years)

Methods:
An aliquot of the pooled plasma and of 0.05 M phosphate buffer (pH 7.0) containing [^{3}H]-formoterol fumarate were mixed to prepare solutions ranging from 0.1 to 100 ng/mL. After incubating 1 hour at 37° C, the solutions were centrifuged at 50,000 rpm for 18 hours to precipitate the proteins. A [redacted] cocktail was added to the supernatant and the radioactivity was measured.

Results:
The binding of unchanged formoterol to plasma proteins was relatively constant across the concentrations tested (0.1 - 100 ng/mL). The mean bound fractions were: 0.1 ng/mL: 64.0% (± 0.5), 1 ng/mL: 63.8% (± 0.5), 10 ng/mL: 61.3% (± 0.6), 100 ng/mL: 63.8% (± 1.1).

Comment Protein binding of only parent formoterol was assessed. The affinity of formoterol's metabolites were not estimated.

Conclusion Plasma protein binding of formoterol is approximately 63% over a concentration range of 0.1 to 100 ng/mL.

APPEARS THIS WAY
ON ORIGINAL

Pharmacokinetics Study with Formoterol Dry Powder Inhalation Capsule via Aeroliser

Study No. 054 **Volume** 1.71-1.72
Investigator [redacted]

Study Dates 3/4/96 - 3/28/96
Analytical Facility [redacted]
Analysis Dates 3/25/96 - 7/17/96

OBJECTIVES To characterize the single-dose plasma pharmacokinetics of formoterol after inhalation and assess the urinary excretion of the enantiomers.

FORMULATIONS
FORADIL 12 µg dry powder capsules for inhalation, Batch T2/95
Aeroliser dry powder capsule inhaler, Batch 5013208

STUDY DESIGN A total of 13 healthy, non-smoking adult male and female volunteers were included in this open-label, single-dose, 1-treatment, 1-period study. Before the trial began, subjects were instructed on the proper use of the Aeroliser inhaler device. After an overnight fast, subjects received a single, 120 µg dose (inhalation of ten 12 µg capsules) of study medication. Volunteers continued fasting and remained ambulatory for 4 hours after study drug administration. At this time, regular meals were served. Subjects were confined throughout the study and abstained from the consumption of xanthine containing foods and beverages. Blood samples were obtained for plasma formoterol determinations just prior to (zero hour), 5, 10, 15, 20, 30 and 45 minutes, and 1, 2, 3, 4, 6, 8, 12, and 24 hours after study drug administration. Urine samples were collected just prior to dosing and at 0-1, 1-2, 2-4, 4-8, 8-12, 12-24, 24-48 and 48-72 intervals after dosing.

ASSAY [redacted] method was used for plasma formoterol determinations. An [redacted] method was used for the assessment of urinary formoterol

Plasma Assay Performance (only summary data were submitted, and are reported below)

Linearity Satisfactory: [redacted]
Accuracy[6] Satisfactory: [redacted]
Precision Satisfactory: [redacted]
Sensitivity LOQ: [redacted]
Specificity Unsatisfactory: [redacted] not submitted

[6] Accuracy and precision based on back-calculation of standard curve data

Urine Assay Performance (only summary data were submitted, and are reported below)

	(R,R)-enantiomer	*(S,S)-enantiomer*
Linearity	Satisfactory: [redacted]	Satisfactory [redacted]
Accuracy[7]	Satisfactory: [redacted]	Satisfactory: [redacted]
Precision	Satisfactory: [redacted]	Satisfactory: [redacted]
Sensitivity	LOQ: [redacted] nmol/L	LOQ: [redacted] nmol/L
Specificity	Satisfactory: [redacted] submitted	Satisfactory: [redacted] submitted

DATA ANALYSIS

Pharmacokinetic: - C_{max}, T_{max}, AUC_0 , $t_{1/2}$[8], $A_e(0\text{-}48)$, and CL_R

Statistical: Descriptive statistics were provided for pharmacokinetic parameter estimates. Additionally, the sponsor investigated the effect of body weight and sex on formoterol exposure, as measured by AUC.

RESULTS A total of 12 subjects (8 male, 4 female) completed the study. The mean plasma concentration versus time profiles for the first 24 hours after dosing are presented in Figure 5. Urinary excretion rates are plotted in Figure 6. Plasma and urine pharmacokinetic parameters are presented in Tables 8 and 9, respectively. Table 10 describes the influence of weight and sex on formoterol exposure (AUC).

Table 8. Mean (%CV) Plasma Formoterol Pharmacokinetic Parameters After a Single 120 µg Dose of Inhaled Formoterol Fumarate

C_{max} (pmol/L)	*t_{max}[9] (hours)*	*AUC (pmol•hr/L)*	*$t_{1/2}$ (hours)*
266 (41)	0.083 (0.083-1)	1330 (30)	10.0 (18)

Table 9. Mean (%CV) Urine Formoterol Pharmacokinetic Parameters After a Single 120 µg Dose of Inhaled Formoterol Fumarate

	(R,R)-enantiomer	*(S,S)-enantiomer*
A_e(% of Dose $_{0\text{-}48hr}$)	3.61 (25)	4.80 (28)
$t_{1/2}$[10] (hr)	13.9 (40)	12.3 (28)

[7] Accuracy and precision based on back-calculation of standard curve data

[8] Based on both urine and plasma pharmacokinetic data

[9] median (range)

[10] As calculated by linear regression analysis of the semilogarithmic excretion rate-time curve between 10 and 36 hours

Figure 5. Mean ± SD (n=12) Formoterol Plasma Concentration versus Time Profile after Inhalation of a Single 120 µg Dose of Formoterol Fumarate

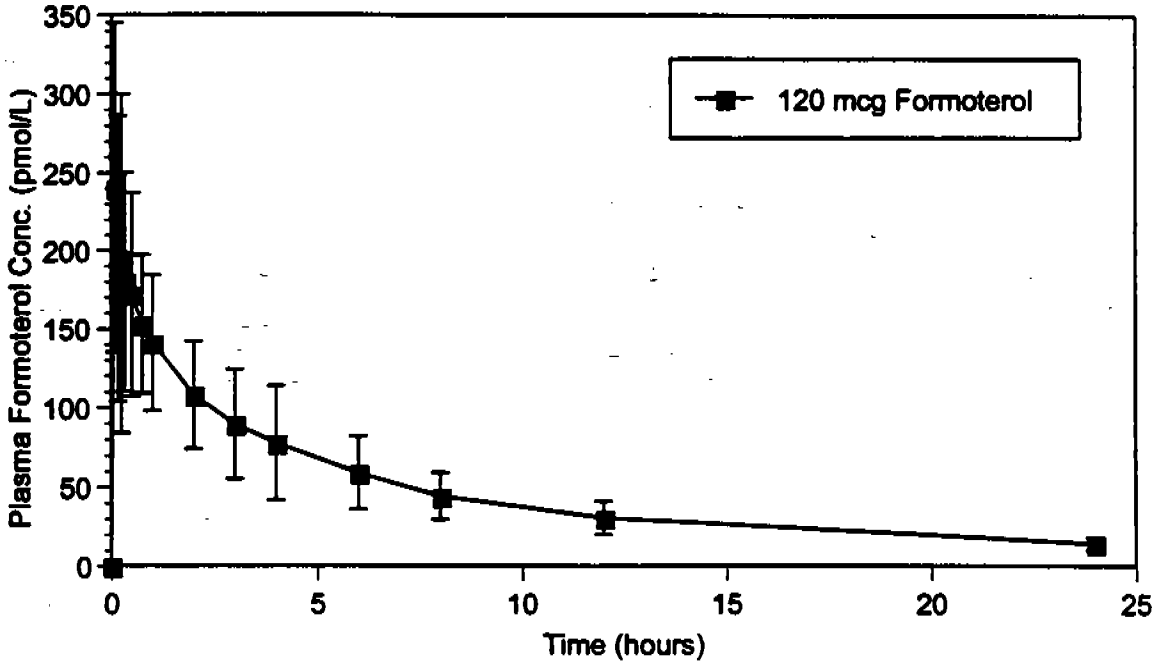


Figure 6. Urinary Excretion Rate of the (R,R) and (S,S)-Enantiomers of Formoterol (nmol/hour)

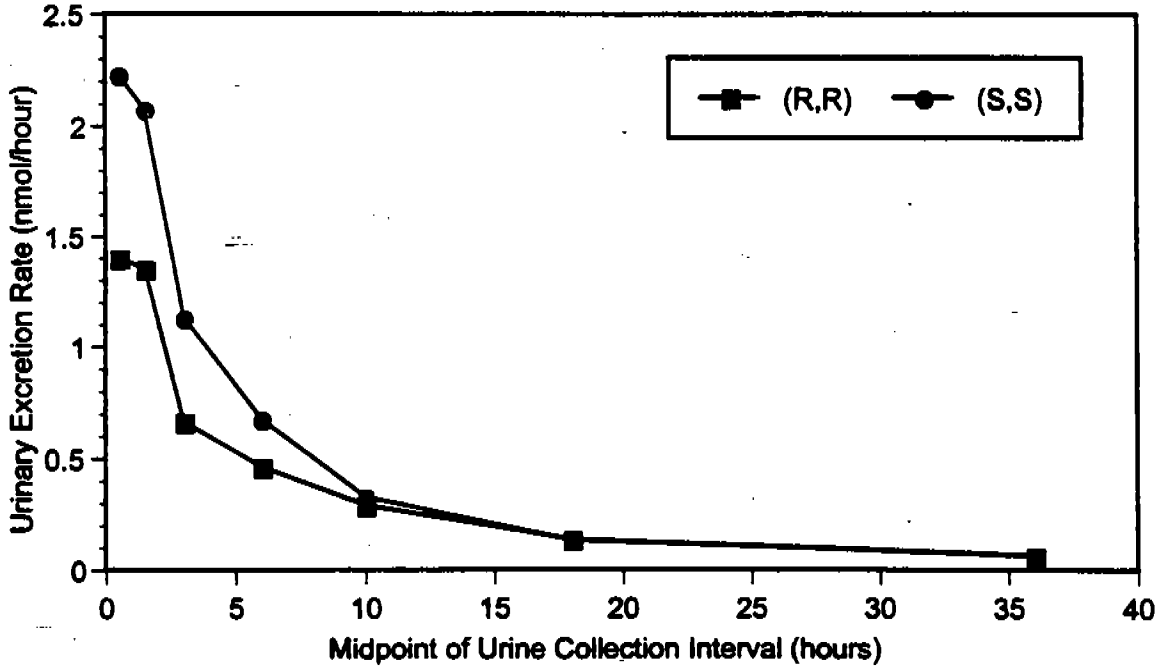


Table 10. The Influence of Subject Weight and Gender on Formoterol Exposure, as Measured by AUC (%CV) After Inhalation of a Single 120 μg Dose

	AUC (pmol•hr/L)	*Body Weight (kg)*	*AUC_{75kg} (pmol•hr/L)*
All Subj. (n=12)	**1330 (30)**	**78.1±12.1**	**1370**
Females (n=4)	**1580 (30)**	**70.1±8.6**	**1480**
Males (n=8)	**1210 (26)**	**82.2±11.9**	**1310**

COMMENTS

1. More meaningful results could have been obtained if the sponsor had measured both unchanged and the conjugated form of formoterol.
2. With regard to the plasma and urine assay performance validation, only summary data were reported. The sponsor is requested to submit data to fully demonstrate the linearity, accuracy, precision and specificity of the method. This should include complete standard curve data, independent quality control results and representative ———— For further details on currently accepted assay validation, the sponsor is referred to: Shah VP, et al. *Pharm Res* Vol 9, No. 4 (1992).

CONCLUSION

After an inhaled 120 μg dose (ten times the proposed clinical dose of 12 μg) of formoterol fumarate dry powder, formoterol was rapidly absorbed and demonstrated an elimination half-life of approximately 10 - 14 hours. Based on urinary excretion data, it appears that the (S,S) enantiomer of formoterol is cleared more rapidly than its (R,R) counterpart. When adjusted for weight, formoterol exposure, as measured by plasma AUC, is approximately 13% greater in female than male subjects.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
DIVISION OF PHARMACEUTICAL EVALUATION II

Date: July 18, 1997

To: Director, Mei-Ling Chen, Ph.D. (HFD-870)
Deputy Director, Mr. John Hunt (HFD-870)

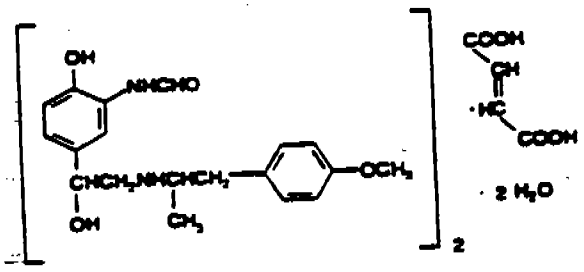
Through: Team Leader, Dale Conner, Pharm.D. (HFD-870) /S/ 7/21/97

From: Tien-Mien Chen, Ph.D. (HFD-870) /S/ 07/21/97

RE: Filing Meeting for NDA 20-831 (Foradil 12-μg Capsule for Inhalation; Formoterol fumarate)

SYNOPSIS:

On 06/24/97, Novartis submitted NDA 20-831 to the Agency for Foradil 12-μg capsule for inhalation (formoterol fumarate). It is an NME and it has a molecular weight of 840.9 and two chiral centers. Its structural formula is shown below:



Formoterol fumarate, a racemate; 50:50 mixture of (-)R,R and (+)S,S-enantiomers, is a white to yellowish powder and is slightly soluble in water. Formoterol is reported as a long-acting, highly selective, β_2-adrenergic agonist. Only one strength is currently sought for approval and it is to be administered by the oral inhalation route only via Aeroliser, a specially designed plastic device for inhaling powder.

For the prevention and maintenance treatment of bronchoconstriction in patients ≥ years of age and older with reversible obstructive airways disease, including patients with symptoms of nocturnal asthma, the recommended dosing regimen is one 12-μg capsule given BID and For the prevention of exercise-induced bronchospasm in patients ≥ years of age and older, one 12-μg capsule is

given at least 15 min before exercise and for patients 12 years of age and older, ——— Please see the proposed package insert in Attachment 1 for details.

Submitted under Human Pharmacokinetics and Bioavailability section of the NDA were 21 pharmacokinetic/bioavailability (PK/Bio) studies. Five are considered to be pivotal for 1) relative bioavailability of capsule comparing to an aerosol solution MDI, 2) single-dose PK in healthy subjects using a high dose (120 μg), 3) in vivo metabolism using ^{3}H-radiolabeled drug, 4) dose-proportionality for 12, 24, 48, and 96 μg doses, and 5) multiple-dose PK for 12 and 24 μg BID in patients. The above pivotal studies employed adult subjects only. Both males and females were used in some studies. Cytochrome P-450 isozymes responsible for O-demethylation of formoterol were identified. Pharmacological activities of all 4 enantiomers were investigated in vitro. PK and pharmacodynamic (PD) relationship was evaluated in the dose-proportionality study. The to-be-marketed formulation was used in most of the pivotal PK studies and clinical trials except for the color of the capsule shell.

As indicted by the sponsor, due to assay limitations, a restricted PK program was performed. Therefore, no studies were submitted for 1) renal or hepatic impaired patients 2) children down to age of 6 years of age, 3) the elderly, 4) drug-drug interaction, and 5) ethnicity.

RECOMMENDATION:

The human PK/Bio section of NDA 20-831 that was submitted on 06/24/97 has been briefly reviewed by the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II). OCPB/DPE II is of the opinion that the NDA is acceptable for filing. The following comments need to be conveyed to the sponsor ASAP.

COMMENTS: (Need to be conveyed to the sponsor)

1. The compositions of the 6- and 24-μg capsule formulations that were used in the PK studies, e.g., No. —— 01, were not provided. Please provide the above information or provide the volume and page no. if it is already submitted.

2. Please provide the composition of formulation(s) and the dose(s) of formoterol capsules used in the clinical trials.

3. What will be the full-scale production batch size for the commercial 12-μg capsules?

cc: NDA 20-831, HFD-570 (Anthracite, Jani), HFD-870 (M. L. Chen, D. Conner, T. M. Chen), CDR (B. Murphy).

NDA 20-831 (Foradil 12-μg Capsule for Inhalation; formoterol furmarate)

Attachment 1:

APPEARS THIS WAY
ON ORIGINAL

Proposed Package Insert (June, 97)

20 PAGE(S) REDACTED

Draft

Labeling